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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 401/12, A61K 31/33, 31/19, A61P 43/00, C07D 257/04, 215/14, 215/18, 217/04, 417/12, 215/12, 403/12, 239/90, 405/12, 241/44, 409/12, 215/60, 231/56, 213/64, 215/22, 307/81, 333/28, 209/18, 209/34, 263/32, 215/38, C07C 233/11, 69/52, 321/28, 57/03, 63/00

A1

(11) International Publication Number: WO 00/64888

(43) International Publication Date: 2 November 2000 (02.11.00)

(21) International Application Number: PCT/US00/11833

(22) International Filing Date: 28 April 2000 (28.04.00)

(30) Priority Data:
60/131,455 28 April 1999 (28.04.99) US

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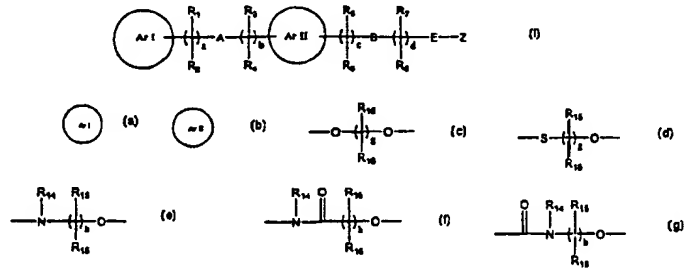
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DI-ARYL ACID DERIVATIVES AS PPAR RECEPTOR LIGANDS



(57) Abstract

This invention is directed to diaryl acid derivatives of formula (I) and their pharmaceutical compositions as PPAR ligand receptor binders. The PPAR ligand receptor binders of this invention are useful as agonists or antagonists of the PPAR receptor wherein: (a) and (b) are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl; A is –O–, –S–, –SO–, SO_2–, $–NR_{13}$–, –C(O)–, $–N(R_{14})C(O)$–, $–C(O)N(R_{15})$–, $–N(R_{14})C(O)N(R_{15})$–, $–C(R_{14})=N$–, (c), (d), (e), a chemical bond, (f) or (g), B is –O–, –S–, $–NR_{19}$– a chemical bond, –C(O)–, $–N(R_{20})C(O)$–, or $–C(O)N(R_{20})$–; Z is $R_{21}O_2C$–, $R_{21}OC$–, cyclo–imide, –CN, $R_{21}O_2SHNCO$–, $R_{21}O_2SHN$–, $(R_{21})_2NCO$–, $R_{21}O$–2,4–thiazolidinedionyl, or tetrazolyl.

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DI-ARYL ACID DERIVATIVES AS PPAR RECEPTOR LIGANDS

Background of the Invention-

This invention is directed to the use of diaryl acid derivatives and their pharmaceutical compositions as PPAR ligand receptor binders. The PPAR ligand receptor binders of this invention are useful as agonists or antagonists of the PPAR receptor.

Field of the Invention

Peroxisome proliferator-activated receptors (PPAR) can be subdivided into three subtypes, namely: PPARα, PPARδ, and PPARγ. These are encoded by different genes (Motojima, Cell Structure and Function, 18:267-277, 1993). Moreover, 2 isoforms of PPARγ also exist, PPARγ$_1$ and γ$_2$. These 2 proteins differ in their NH_2 -terminal-30 amino acids and are the result of alternative promoter usage and differential mRNA splicing (Vidal-Puig, Jimenez, Linan, Lowell, Hamann, Hu, Spiegelman, Flier, Moller, J. Clin. Invest., 97:2553-2561, 1996).

Biological processes modulated by PPAR are those modulated by receptors, or receptor combinations, which are responsive to the PPAR receptor ligands described herein. These processes include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinism (resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and /or autoimmune hypoglycemia due to autoantibodies to insulin, the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, adipocyte differentiation.

Obesity is an excessive accumulation of adipose tissue. Recent work in this area indicates that PPARγ plays a central role in the adipocyte gene expression and differentiation. Excess adipose tissue is associated with the development of serious medical conditions, for example, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, coronary artery disease, hyperlipidemia obesity and certain malignancies. The adipocyte may also influence glucose homeostasis through the production of tumor necrosis factor α (TNFα) and other molecules.

Non-insulin-dependent diabetes mellitus (NIDDM), or Type II diabetes, is the more common form of diabetes, with 90-95% of hyperglycemic patients experiencing this form of the disease. In NIDDM there appears to be a reduction in the pancreatic β-cell mass, several distinct defects in insulin secretion or a decrease in tissue sensitivity to insulin. The symptoms of this form of diabetes include fatigue, frequent urination, thirst, blurred vision, frequent infections and slow healing of sores, diabetic nerve damage and renal disease.

Resistance to the metabolic actions of insulin is one of the key features of non-insulin dependent diabetes (NIDDM). Insulin resistance is characterised by impaired uptake and utilization of glucose in insulin-sensitive target organs, for example, adipocytes and skeletal muscle, and by impaired inhibition of hepatic glucose output. The functional insulin deficiency and the failure of insulin to supress hepatic glucose output results in fasting hyperglycemia. Pancreatic β-cells compensate for the insulin resistance by secreting increased levels of insulin. However, the β-cells are unable to maintain this high output of insulin, and, eventually, the glucose-induced insulin secretion falls, leading to the deterioration of glucose homeostasis and to the subsequent development of overt diabetes.

Hyperinsulinemia is also linked to insulin resistance, hypertriglyceridaemia and increased plasma concentration of low density lipoproteins. The association of insulin resistance and hyperinsulinemia with these metabolic disorders has been termed "Syndrome X" and has been strongly linked to an increased risk of hypertension and coronary artery disease.

Metformin is known in the art to be used in the treatment of diabetes in humans (US Patent No. 3,174,901). Metformin acts primarily to decrease liver glucose production. Troglitazone® is known to work primarily on enhancing the ability of skeletal muscle to respond to insulin and take up glucose. It is known that combination therapy comprising metformin and troglitazone can be used in the treatment of abnormalities associated with diabetes (DDT 3:79-88, 1998).

PPAR γ activators, in particular Troglitazone®, have been found to convert cancerous tissue to normal cells in liposarcoma, a tumor of fat (PNAS 96:3951-3956, 1999). Furthermore, it has been suggested that PPAR γ activators may be useful in the treatment of breast and colon cancer (PNAS 95:8806-8811, 1998, Nature Medicine 4:1046-1052, 1998).

Moreover, PPARγ activators, for example Troglitazone®, have been implicated in the treatment of polycystic ovary syndrome (PCO). This is a syndrome in women that is characterized by chronic anovulation and hyperandrogenism. Women with this syndrome often have insulin resistance and an increased risk for the development of noninsulin-dependent diabetes mellitus. (Dunaif, Scott, Finegood, Quintana, Whitcomb, J. Clin. Endocrinol. Metab., 81:3299, 1996.

Furthermore, PPARγ activators have recently been discovered to increase the production of progesterone and inhibit steroidogenesis in granulosa cell cultures and therefore may be useful in the treatment of climacteric. (United States Patent 5,814,647 Urban et al. September 29, 1998; B. Lohrke et al. Journal of Edocrinology, 159, 429-39, 1998). Climacteric is defined as the syndrome of endocrine, somatic and psychological changes occurring at the termination of the reproductive period in the female.

Peroxisomes are cellular organelles which play a role in controlling the redox potential and oxidative stress of cells by metabolizing a variety of substrates such as hydrogen peroxide. There are a number of disorders associated with oxidative stress. For example, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury (shock), doxorubicin-induced

cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hyperoxic lung injuries, are each associated with the production of reactive oxygen species and a change in the reductive capacity of the cell. Therefore, it is envisaged that PPARα activators, among other things, regulate the redox potential and oxidative stress in cells, would be effective in the treatment of these disorders (Poynter et al, J. Biol. Chem. 273, 32833-41, 1998).

It has also been discovered that PPARα agonists inhibit NFκB-mediated transcription thereby modulating various inflammatory responses such as the inducible nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) enzyme pathways (Pineda-Torra, I. T al, 1999, Curr. Opinion in Lipidology, 10,151-9) and thus can be used in the therapeutic intervention of a wide variety of inflammatory diseases and other pathologies (Colville-Nash, et al., Journal of Immunology, 161, 978-84, 1998; Staels et al, Nature, 393, 790-3, 1998).

Peroxisome proliferators activate PPAR , which in turn, acts as a transcription factor, and causes differentiation, cell growth and proliferation of peroxisomes. PPAR activators are also thought to play a role in hyperplasia and carcinogenesis as well as altering the enzymatic capability of animal cells, such as rodent cells, but these PPAR activators appear to have minimal negative effects in human cells (Green, Biochem. Pharm. 43(3):393, 1992). Activation of PPAR results in the rapid increase of gamma glutamyl transpeptidase and catalase.

PPARα is activated by a number of medium and long-chain fatty acids and is involved in stimulating β-oxidation of fatty acids in tissues such as liver, heart, skeletal muscle, and brown adipose tissue (Isseman and Green, supra; Beck et al., Proc. R. Soc. Lond. 247:83-87, 1992; Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657, 1992). Pharmacological PPARα activators, for example fenofibrate, clofibrate, genfibrozil, and bezafibrate, are also involved in substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia, hyperlipidemia and obesity. PPARα is also known to be involved in inflammatory disorders. (Schoonjans, K., Current Opionion in Lipidology, 8, 159-66, 1997).

The human nuclear receptor PPARδ has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., Molecular Endocrinology, 6:1634-1641 (1992), the contents of which are hereby incorporated herein by reference. It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor. For example, in A. Schmidt et al., Molecular Endocrinology, 6: pp. 1634-1641, 1992, the receptor is referred to as NUC1. PPARδ is observed in both embryo and adult tissues. This receptor has been reported to be involved in regulating the expression of some fat-specific genes, and plays a role in the adipogenic process (Amri, E. et al., J. Biol. Chem. 270, 2367-71, 1995).

Atherosclerotic disease is known to be caused by a number of factors, for example, hypertension, diabetes, low levels of high density lipoprotein (HDL), and high levels of low density lipoprotein (LDL).

In addition to risk reduction via effects on plasma lipid concentrations and other risk factors, PPARα agonists exert direct atheroprotective effects (Frick, M. H.,et al. 1997.. Circulation 96:2137-2143, de Faire, et al. 1997. Cardiovasc. Drugs Ther. 11 Suppl 1:257-63:257-263).

It has recently been discovered that PPARδ agonists are useful in raising HDL levels and therefore useful in treating atherosclerotic diseases. (Leibowitz et al.; WO/9728149). Atherosclerotic diseases include vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease. Coronary heart disease includes CHD death, myocardial infarction, and coronary revascularization. Cerebrovascular disease includes ischemic or hemorrhagic stroke and transient ischemic attacks.

PPARγ subtypes are involved in activating adipocyte differentiation, and are not involved in stimulating peroxisome proliferation in the liver. Activation of PPARγ is implicated in adipocyte differentiation through the activation of adipocyte-specific gene expression (Lehmann, Moore, Smith-Oliver, Wilkison, Willson, Kliewer, J. Biol. Chem., 270:12953-12956, 1995). The DNA sequences for the PPARγ receptors are described in Elbrecht et al., BBRC 224;431-437 (1996). Although peroxisome proliferators, including fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives such as the arachidonic acid metabolite 15-deoxy-delta^{12},14 -prostaglandin J_2 (15d-PGJ_2) have been identified as natural ligands specific for the PPARγ subtype, which also binds thiazolidinediones.This prostaglandin activates PPARγ-dependent adipogenesis, but activates PPARα only at high concentrations (Forman, Tontonoz, Chen, Brun, Spiegelman, Evans, Cell, 83:803-812, 1995; Kliewer, Lenhard, Wilson, Patel, Morris, Lehman. Cell, 83:813-819, 1995). This is further evidence that the PPAR family subtypes are distinct from one another in their pharmacological response to ligands.

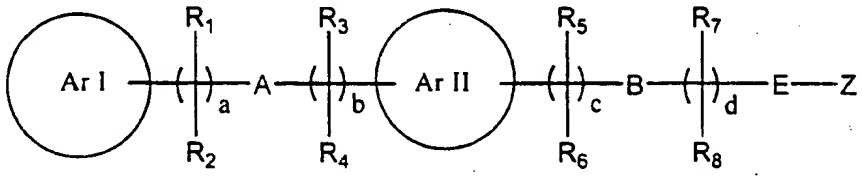
It has been suggested that compounds activating both PPARα and PPARγ should be potent hypotriglyceridemic drugs, which could be used in the treatment of dyslipidemia associated with atherosclerosis, non-insulin dependent diabetes mellitus,Syndrome X,. (Staels, B. et al., Curr. Pharm. Des., 3 (1), 1-14 (1997)) and familial combined hyperlipidemia (FCH). Syndrome X is the syndrome characterized by an initial insulin resistant state, generating hyperinsulinaemia, dyslipidaemia and impaired glucose tolerance, which can progress to non-insulin dependent diabetes mellitus (Type II diabetes), characterized by hyperglycemia. FCH is characterized by hypercholesterolemia and hypertriglyceridemia within the same patient and family.

The present invention is directed to a series of compounds that are useful in modulating PPAR receptors, as well as to a number of other pharmaceutical uses associated therewith.

Summary of the Invention

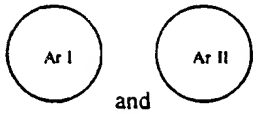
This invention provides new aromatic compounds and pharmaceutical compositions prepared therewith that are PPAR ligand receptor binders, and which are useful as agonists or antagonists of the PPAR receptors. The invention also includes the discovery of new uses for previously known compounds.

The compounds for use according to the invention, including the new compounds of the present invention, are of Formula I



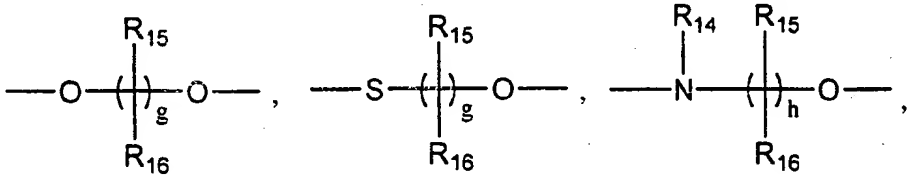
(I)

wherein:

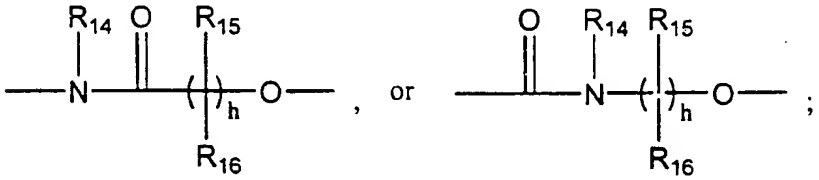


and are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is -O-, -S-, -SO-, -SO_2-, -NR_{13}-, -C(O)-, -$N(R_{14})C(O)$-, -$C(O)N(R_{15})$-, -$N(R_{14})C(O)N(R_{15})$-, -$C(R_{14})$=N-,



a chemical bond,



;

B is –O-, -S-, -NR_{19}-, a chemical bond, -C(O)-, -$N(R_{20})C(O)$-, or –$C(O)N(R_{20})$-;

E is a chemical bond or an ethylene group;

a is 0-6;

b is 0-4;

c is 0-4;

d is 0-6;

g is 1-5;

h is 1-4;

R_1, R_3, R_5 and R_7, are independently hydrogen, halogen, alkyl, carboxyl, alkoxycarbonyl or aralkyl;

R_2, R_4, R_6 and R_8, are independently -$(CH_2)_q$-X;

q is 0-3;

X is hydrogen, halogen, alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, carboxyl, alkoxycarbonyl, tetrazolyl, acyl, acylHNSO$_2$-, -SR_{23}, Y^1Y^2N- or Y^3Y^4NCO-;

Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of Y^1 and Y^2 is hydrogen or alkyl and the other of Y^1 and Y^2 is acyl or aroyl;

Y^3 and Y^4 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl;

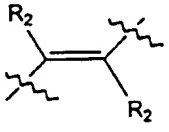
Z is $R_{21}O_2C$-, $R_{21}OC$-, cyclo-imide, -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$-, $R_{21}O$- 2,4-thiazolidinedionyl, or tetrazolyl; and

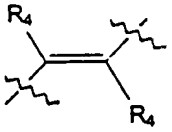
R_{19} and R_{21} are independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

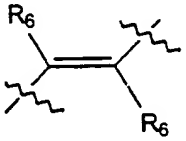
R_{13}, R_{17}, R_{19} and R_{23} are independently $R_{22}OC$-, $R_{22}NHOC$-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl;

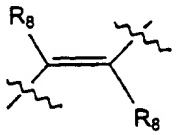
R_{14}, R_{15}, R_{16}, R_{18} and R_{20} are independently hydrogen, alkyl, aralkyl, carbonyl, or alkoxycarbonyl;

or R_{14} and R_{15} taken together with the carbon and nitrogen atoms through which they are linked form a 5 or 6-membered azaheterocyclyl group; or

when a is 2-6, then at least one pair of vicinal R_1 radicals taken together with the carbon atoms to which the R_1 radicals are linked form a  group; or

when b is 2-4, then at least one pair of vicinal R_3 radicals taken together with the carbon atoms to which the R_3 radicals are linked form a  group; or

when c is 2-4, then at least one pair of vicinal R_5 radicals taken together with the carbon atoms to which the R_5 radicals are linked form a  group; or

when d is 2-6, then at least one pair of vicinal R_7 radicals taken together with the carbon atoms to which the R_7 radicals are linked form a  group, or a 5-membered cycloalkyl group; or

when d is 2-6, then at least one pair of non-vicinal R_7 radicals taken together with the carbon atoms to which the R_7 radicals are linked form a 5-membered cycloalkyl group; or

geminal R_5 and R_6 radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; or

geminal R_7 and R_8 radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; and

R_{22} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

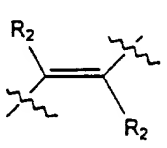
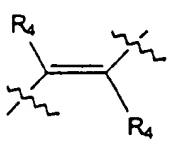
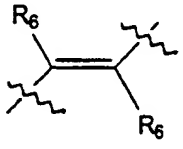
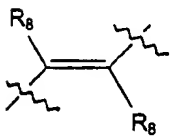
As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

In the present specification, the term "compounds for use according to the invention", and equivalent expressions, are meant to embrace compounds of general Formula (I) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula (I), including N-oxides thereof. For example an ester of a compound of Formula (I) containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of Formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule.

"Patient" includes both human and other mammals.

In the present invention, the moiety "  ,  ,  , or  "encompasses both the syn and anti configurations.

"Chemical bond" means a direct single bond between atoms.

"Acyl" means an H-CO- or alkyl-CO- group wherein the alkyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain, which may be straight or branched. The alkenyl group is optionally substituted by one or more halo groups. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl and decenyl.

"Alkoxy" means an alkyl-O- group wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"Alkoxycarbonyl" means an alkyl-O-CO- group, wherein the alkyl group is as herein defined. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, or t-butyloxycarbonyl.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 13 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain, which may be straight or branched. The alkyl is optionally substituted with one or more "alkyl group substituents" which may be the same or different, and include halo, carboxy, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, alkoxy, alkoxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, Y^1Y^2NCO-, wherein Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or Y^1 and Y^2 taken together with the nitrogen atom to which Y^1 and Y^2 are attached form heterocyclyl. Exemplary alkyl groups include methyl, trifluoromethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, and 3-pentyl.Preferably, the alkyl group substituent is selected from acyl, carboxy, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, and pyridylmethyloxycarbonylmethyl and alkoxycarbonyl.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulfonyl" means an alkyl-SO_2-group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylthio" means an alkyl-S- group wherein the alkyl group is as defined above. Exemplary alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Aralkoxy" means an aralkyl-O- group wherein the aralkyl group is as defined herein. Exemplary aralkoxy groups include benzyloxy and 1- and 2-naphthalenemethoxy.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group wherein the aralkyl group is as defined herein. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Aralkyl" means an aryl-alkyl- group wherein the aryl and alkyl groups are as defined herein. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthalenemethyl.

"Aralkylsulfonyl" means an aralkyl-SO_2- group wherein the aralkyl group is as defined herein.

"Aralkylsulfinyl" means an aralkyl-SO- group wherein the aralkyl group is as defined herein.

"Aralkylthio" means an aralkyl-S- group wherein the aralkyl group is as defined herein. An exemplary aralkylthio group is benzylthio.

"Aroyl" means an aryl-CO- group wherein the aryl group is as defined herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. The aryl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Exemplary aryl groups include phenyl, naphthyl, substituted phenyl, and substituted naphthyl.

"Aryldiazo" means an aryl-diazo- group wherein the aryl and diazo groups are as defined herein.

"Fused arylcycloalkenyl" means a fused aryl and cycloalkenyl as defined herein. Preferred fused arylcycloalkenyls are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkenyl group may be bonded to the rest of the compound through any atom of the fused system capable of such bondage. The fused arylcycloalkenyl may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. Exemplary fused arylcycloalkenyl groups include 1,2-dihydronaphthylenyl; indenyl; 1,4-naphthoquinonyl, and the like.

"Fused arylcycloalkyl" means a fused aryl and cycloalkyl as defined herein. Preferred fused arylcycloalkyls are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkyl group may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The fused arylcycloalkyl may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. Exemplary fused arylcycloalkyl groups include 1,2,3,4-tetrahydronaphthylenyl; 1,4-dimethyl-2,3-dihydronaphthalenyl; 2,3-dihydro-1,4-naphthoquinonyl, α-tetralonyl, and the like.

"Fused arylheterocyclenyl" means a fused aryl and heterocyclenyl wherein the aryl and heterocyclenyl groups are as defined herein. Preferred fused arylheterocyclenyl groups are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclenyl group may be bonded to the rest of the compound through any atom of the fused

system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heterocyclenyl portion of the fused arylheterocyclenyl means that a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. The fused arylheterocyclenyl may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused arylheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclenyl portion of the fused arylheterocyclenyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclenyl include 3H-indolinyl, 2(1H)quinolinonyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, (2H)quinolinyl N-oxide, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, chromonyl, 3,4-dihydroisoquinoxalinyl, 4-(3H)quinazolinonyl, 4H-chromen-2yl, and the like. Preferably, 2(1H)quinolinonyl, 1,2-dihydroquinolinyl, (2H)quinolinyl N-oxide, or 4-(3H)quinazolinonyl.

"Fused arylheterocyclyl" means a fused aryl and heterocyclyl wherein the aryl and heterocyclyl groups are as defined herein. Preferred fused arylheterocyclyls are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclyl may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heterocyclyl portion of the fused arylheterocyclyl means that a nitrogen, oxygen or sulphur atom respectively is present as a ring atom. The fused arylheterocyclyl group may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused arylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclyl portion of the fused arylheterocyclyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 1H-2,3-dihydroisoindol-2-yl. 2,3-dihydrobenz[f]isoindol-2-yl, 1,2,3,4-tetrahydrobenz[g]isoquinolin-2-yl, chromanyl, isochromanonyl, 2,3-dihydrochromonyl, 1,4-benzodioxan, 1,2,3,4-tetrahydroquinoxalinyl, and the like. Preferably , 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinoxalinyl, and 1,2,3,4-tetrahydroquinolinyl.

"Aryloxy" means an aryl-O- group wherein the aryl group is as defined herein. Exemplary groups include phenoxy and 2-naphthyloxy.

"Aryloxycarbonyl" means an aryl-O-CO- group wherein the aryl group is as defined herein. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfonyl" means an aryl-SO_2- group wherein the aryl group is as defined herein.

"Arylsulfinyl" means an aryl-SO- group wherein the aryl group is as defined herein.

"Arylthio" means an aryl-S- group wherein the aryl group is as defined herein. Exemplary arylthio groups include phenylthio and naphthylthio.

"Carbamoyl" is an NH_2-CO- group.

"Carboxy" means a HO(O)C- (carboxylic acid) group.

"Compounds of the invention," and equivalent expressions, are meant to embrace compounds of general Formula (I) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

"Cycloalkoxy" means an cycloalkyl-O- group wherein the cycloalkyl group is as defined herein . Exemplary cycloalkoxy groups include cyclopentyloxy and cyclohexyloxy.

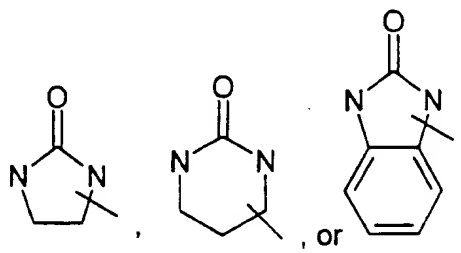
"Cycloalkyl-alkoxy" means an cycloalkyl-alkylene-O- group wherein the cycloalkyl group and alkylene group are as defined herein . Exemplary cycloalkyl-alkoxy groups include cyclopentylmethylene-oxy and cyclohexylmethylene-oxy.

"Cycloalkenyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The cycloalkenyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Exemplary monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. An exemplary multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The cycloalkyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Exemplary monocyclic cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Exemplary multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl, and the like.

"Cycloalkylene" means a bivalent, saturated carbocyclic group having about 3 to about 6 carbon atoms. Preferred cycloalkylene groups include 1,1-, 1,2-, 1,3-, and 1,4- cis or trans-cyclohexylene, and 1,1-, 1,2-, and 1,3-cyclopentylene.

"Cyclo-imide" means a compound of formulae



The cyclo-imide moiety may be attached to the parent molecule through either a carbon atom or nitrogen atom of the carbamoyl moiety. An exemplary imide group is N-phthalimide.

"Diazo" means a bivalent -N=N- radical.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro and bromo, more preferably fluoro and chloro.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro and bromo, more preferably fluoro and chloro.

"Heteroaralkyl" means a heteroaryl-alkyl- group wherein the heteroaryl and alkyl groups are as defined herein. Preferred heteroaralkyls contain a lower alkyl moiety. Exemplary heteroaralkyl groups include thienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

"Heteroaralkylthio" means a heteroaralkyl-S- group wherein the heteroaralkyl group is as defined herein. An exemplary heteroaralkylthio group is 3-pyridinepropanthiol.

"Heteroaralkoxy" means an heteroaralkyl-O- group wherein the heteroaralkyl group is as defined herein. An exemplary heteroaralkoxy group is 4-pyridylmethyloxy.

"Heteroaroyl" means an means an heteroaryl-CO- group wherein the heteroaryl group is as defined herein. Exemplary heteroaryl groups include thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl and 1- and 2-naphthoyl and pyridinoyl.

"Heteroaryldiazo" means an heteroaryl-diazo- group wherein the heteroaryl and diazo groups are as defined herein.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which at least one of the carbon atoms in the ring system is replaced by a hetero atom, i.e., other than carbon, for example nitrogen, oxygen or sulfur. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The heteroaryl ring is optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The designation of aza, oxa or thia as a prefix before the heteroaryl means that a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. A nitrogen atom of an heteroaryl may be a basic nitrogen atom and also may be optionally oxidized to the corresponding N-oxide. Exemplary heteroaryl and substituted heteroaryl groups include pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, cinnolinyl, pteridinyl, benzofuryl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, indazolyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, naphthyridinyl, benzoazaindole, 1,2,4-triazinyl, benzothiazolyl, furyl, imidazolyl, indolyl, isoindolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl. Preferred heteroaryl and substituted heteroaryl groups include quinolinyl,

indazolyl, indolyl, quinazolinyl, pyridyl, pyrimidinyl, furyl, benzothiazolyl, quinoxalinyl, benzimidazolyl, benzothienyl, and isoquinolinyl.

"Fused heteroarylcycloalkenyl" means a fused heteroaryl and cycloalkenyl wherein the heteroaryl and cycloalkenyl groups are as defined herein. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused heteroarylcycloalkenyl may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heteroaryl portion of the fused heteroarylcycloalkenyl means that a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The fused heteroarylcycloalkenyl may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylcycloalkenyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkenyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkenyl groups include 5,6-dihydroquinolyl; 5,6-dihydroisoquinolyl; 5,6-dihydroquinoxalinyl; 5,6-dihydroquinazolinyl; 4,5-dihydro-1H-benzimidazolyl; 4,5-dihydrobenzoxazolyl; 1,4-naphthoquinolyl, and the like.

"Fused heteroarylcycloalkyl" means a fused heteroaryl and cycloalkyl wherein the heteraryl and cycloalkyl groups are as defined herein. Preferred fused heteroarylcycloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused heteroarylcycloalkyl may be bonded to the rest of the compoun through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heteroaryl portion of the fused heteroarylcycloalkyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylcycloalkyl may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylcycloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkyl include 5,6,7,8-tetrahydroquinolinyl; 5,6,7,8-tetrahydroisoquinolyl; 5,6,7,8-tetrahydroquinoxalinyl; 5,6,7,8-tetrahydroquinazolyl; 4,5,6,7-tetrahydro-1H-benzimidazolyl; 4,5,6,7-tetrahydrobenzoxazolyl; 1H-4-oxa-1,5-diazanaphthalen-2-only; 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, 2,3-dihydro-1,4-dinaphthoquinonyl and the like, preferably, 5,6,7,8-tetrahydroquinolinyl or 5,6,7,8-tetrahydroisoquinolyl.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl wherein the heteraryl and heterocyclenyl groups are as defined herein. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclenyl may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heteroaryl or heterocyclenyl portion of the fused

heteroarylheterocyclenyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylheterocyclenyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclenyl groups include 7,8-dihydro[1,7]naphthyridinyl; 1,2-dihydro[2,7]naphthyridinyl; 6,7-dihydro-3H-imidazo[4,5-c]pyridyl; 1,2-dihydro-1,5-naphthyridinyl; 1,2-dihydro-1,6-naphthyridinyl; 1,2-dihydro-1,7-naphthyridinyl; 1,2-dihydro-1,8-naphthyridinyl; 1,2-dihydro-2,6-naphthyridinyl, and the like.

"Fused heteroarylheterocyclyl" means a fused heteroaryl and heterocyclyl wherein the heteroaryl and heterocyclyl groups are as defined herein. Preferred fused heteroarylheterocyclyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclyl may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylheterocyclyl may be optionally substituted by one or more ring system substituent, wherein the "ring system substituent" is as defined herein. The nitrogen atom of a fused heteroarylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclyl groups include 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl; 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl; 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl; 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2yl; 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl. 2,3,-dihydro-1H-pyrrolo[3,4-b]indol-2-yl; 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl; 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl; 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2 yl, 5,6,7,8-tetrahydro[1,7]napthyridinyl; 1,2,3,4-tetrhydro[2,7]naphthyridyl; 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl; 2,3-dihydro[1,4]dioxino[2,3-b]pryidyl; 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl; 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl; 6,7-dihydro[5,8]diazanaphthalenyl; 1,2,3,4-tetrahydro[1,5] napthyridinyl; 1,2,3,4-tetrahydro[1,6]napthyridinyl; 1,2,3,4-tetrahydro[1,7]napthyridinyl; 1,2,3,4-tetrahydro[1,8]napthyridinyl; 1,2,3,4-tetrahydro[2,6]napthyridinyl, and the like.

"Heteroarylsulfonyl" means an heteroaryl-SO_2- group wherein the heteroaryl group is as defined herein. An examplary heterarylsulfonyl groups is 3-pyridinepropansulfonyl.

"Heteroarylsulfinyl" means an heteroaryl -SO- group wherein the heteroaryl group is as defined herein.

"Heteroarylthio" means an heteroaryl -S- group wherein the heteroaryl group is as defined herein. Exemplary heteroaryl thio groups include pyridylthio and quinolinylthio.

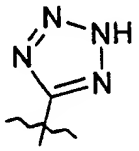
"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which at least one or more of the carbon atoms in the ring system is replaced by a hetero atom, for example a nitrogen, oxygen or sulfur atom, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of aza, oxa or thia as a prefix before the heterocyclenyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclenyl may be optionally substituted by one or more ring system substituents, wherein the "ring system substituent" is as defined herein. The nitrogen atom of an heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclenyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2*H*-pyran, dihydrofuryl, and fluorodihydrofuryl An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Exemplary monocyclic thiaheterocycleny rings include dihydrothiophenyl and dihydrothiopyranyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which at least one of the carbon atoms in the ring system is replaced by a hetero atom, for example nitrogen, oxygen or sulfur. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of aza, oxa or thia as a prefix before the heterocyclyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclyl may be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen atom of an heterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuryl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. Exemplary multicyclic heterocyclyl rings include 1,4 diazabicyclo-[2.2.2]octane and 1,2-cyclohexanedicarboxylic acid anhydride.

"Ring system substituent" includes hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aryloxy, aralkoxy, cycloalkylalkyloxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, fused cycloalkyl, fused cycloalkenyl, fused heterocyclyl, fused

heterocyclenyl, arylazo, heteroarylazo, R^aR^bN-, R^cR^dNCO-, R^cO_2CN-, and $R^cR^dNSO_2$- wherein R^a and R^b are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of R^a and R^b is hydrogen or alkyl and the other of R^a and R^b is aroyl or heteroaroyl. R^c and R^d are independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aralkyl or heteroaralkyl. Where the ring is cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl, the ring system substituent may also include methylene (H_2C=), oxo (O=), thioxo (S=), on carbon atom(s) thereof. Preferably, the ring substituents are selected from oxo (O=), alkyl, aryl, alkoxy, aralkoxy, halo, carboxy, alkoxycarbonyl, and R^cO_2CN-, wherein R^c is cycloalkyl.

"Tetrazolyl" means a group of formula



wherein the hydrogen atom thereof is optionally replaced by alkyl, carboxyalkyl or alkoxycarbonylalkyl.

"PPAR ligand receptor binder" means a ligand which binds to the PPAR receptor. PPAR ligand receptor binders of this invention are useful as agonists or antagonists of the PPAR-α, PPAR-δ, or PPAR-γ receptor.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. A salt can be prepared *in situ* during the final isolation and purification of a compound or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, laurylsulphonate salts, and the like. (See, for example S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66: 1-19, 1977, the contents of which are hereby incorporated herein by reference.)

"Treating" means the partial or complete relieving or preventing of one or more physiological or biochemical parameters associated with PPAR activity.

The term "modulate" refers to the ability of a compound to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of a ligand from a precursor) induce expression of gene(s) maintained under hormone control, or to repress expression of gene (s) maintained under such control.

The term "obesity" refers generally to individuals who are at least about 20-30% over the average weight for the person's age, sex and height. Technically, "obese" is defined, for males, as individuals whose body mass index is greater than 27.3 kg/m^2. Those skilled in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Indeed, the invention method

can also be advantageously practiced by individuals who fall outside of these traditional criteria, for example by those who are prone to obesity.

The phrase "amount effective to lower blood glucose levels" refers to levels of a compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10nM up to 2μM, with concentrations in the range of about 100nm up to about 500nM being preferred.

The phrase "amount effective to lower triclyceride levels" refers to levels of a compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10nM up to 2μM; with concentrations in the range of about 100nm up to about 500nM being preferred.

Preferred Embodiments

Preferred embodiments according to the invention includes the use of compounds of Formula I (and their pharmaceutical compositions) as binders for PPAR receptors.

More particularly, the use of compounds of Formula I that bind to the PPAR-α receptor,

compounds of Formula I that bind to the PPAR-δ receptor,

compounds of Formula I that bind to the PPAR-γ receptor,

compounds of Formula I that bind to the PPAR-α and the PPAR-γ receptor,

compounds of Formula I that bind to the PPAR-α and the PPAR-δ receptor,

compounds of Formula I that bind to the PPAR-γ and the PPAR-δ receptor,

compounds of Formula I that act as PPAR receptor agonists,

compounds of Formula I that act as PPAR-α receptor agonists,

compounds of Formula I that act as PPAR-δ receptor agonists,

compounds of Formula I that act as PPAR-γ receptor agonists,

compounds of Formula I that act as both PPAR-α and PPAR-γ receptor agonists,

compounds of Formula I that act as both PPAR-α and PPAR-δ receptor agonists,

compounds of Formula I that act as both PPAR-γ and PPAR-δ receptor agonists,

compounds of Formula I that act as both PPAR-α receptor antagonists and PPAR-γ receptor agonists,

compounds of Formula I that act as both PPAR-α receptor antagonists and PPAR-δ receptor agonists,

compounds of Formula I and act as both PPAR-γ receptor antagonists and PPAR-δ receptor agonists,

compounds of Formula I that act as both PPAR-α receptor agonists and PPAR-γ receptor antagonists,

compounds of Formula I that act as both PPAR-α receptor agonists and PPAR-δ receptor antagonists,

compounds of Formula I that act as both PPAR-γ receptor agonists and PPAR-δ receptor antagonists,

compounds of Formula I that act as PPAR receptor antagonists,

compounds of Formula I that act as PPAR-α receptor antagonists,

compounds of Formula I that act as PPAR-δ receptor antagonists,

compounds of Formula I that act as PPAR-γ receptor antagonists.

compounds of Formula I that act as both PPAR-α and PPAR-γ receptor antagonists,

compounds of Formula I that act as both PPAR-α and PPAR-δ receptor antagonists, and

compounds of Formula I that act as both PPAR-γ and PPAR-δ receptor antagonists.

An embodiment according to the invention is directed to treating a patient suffering from a physiological disorder capable of being modulated by a compound of Formula I having PPAR ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound, or a pharmaceutically acceptable salt thereof. Physiological disorders capable of being so modulated include, for example, cell differentiation to produce lipid accumulating cells, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinism (resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and /or autoimmune hypoglycemia due to autoantibodies to insulin, autoantibodies to the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which leads to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, adipocyte gene expression, adipocyte differentiation, reduction in the pancreatic β-cell mass, insulin secretion, tissue sensitivity to insulin, liposarcoma cell growth, chronic anovulation, hyperandrogenism, progesterone production, steroidogenesis, redox potential and oxidative stress in cells, nitric oxide synthase (NOS) production, increascd gamma glutamyl transpeptidase, catalase, plasma triglycerides, HDL and LDL cholesterol levels and the like.

Another embodiment according to the invention is directed to a method of treating a disease state in a patient with a pharmaceutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the disease is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids (FFA), or triclycerides.

An embodiment according to the invention is directed to treating a patient suffering from a physiological disorder associated with physiologically detrimental levels of triclycerides in the blood, by administering to the patient a pharmaceutically effective amount of the compound, or of a pharmaceutically acceptable salt thereof.

An embodiment according to the invention is the use of compounds of Formula I and their pharmaceutical compositions as anti-diabetic, anti-lipidemic, anti-hypertensive or anti-arteriosclerotic agents, or in the treatment of obesity.

Another embodiment according to the invention is directed to a method of treating hyperglycemia in a patient, by administering to the patient a pharmaceutically effective amount to lower blood glucose levels of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Preferably, the form of hyperglycemia treated in accordance with this invention is Type II diabetes.

Another embodiment according to the invention is directed to a method of reducing triglyceride levels in a patient, comprising administering to the patient a therapeutically effective amount (to lower triglyceride levels) of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to a method of treating hyperinsulinism in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to a method of treating insulin resistance in a patient. comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to a method of treating cardiovascular disease, such as atherosclerosis in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating of hyperlipidemia in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating of hypertension in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating eating disorders in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Treatment of eating disorders includes the regulation of appetite andor food intake in patients suffering from under-eating disorders such as anorexia nervosa as well as over-eating disorders such as obesity and anorexia bulimia.

Another embodiment according to the invention is directed to treating a disease state associated with low levels of HDL comprising administering to the patient a therapeutically effective amount of a compound of Formula I. or a pharmaceutically acceptable salt thereof. Diseases associated with low levels of HDL include atherosclerotic diseases.

Another embodiment according to the invention is directed to treating polycystic ovary syndrome comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating climacteric comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating inflammatory diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease (emphysema or chronic bronchitis), or asthma comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is to provide a novel pharmaceutical composition which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

In another aspect, the present invention provides a method for treating a disease state in a patient, wherein the disease is associated with a physiological detrimental level of insulin, glucose, free fatty acids (FFA), or triglycerides, in the blood, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, and also administering a therapeutically effective amount of an additional hypoglycemic agent.

In another aspect, the present invention provides a method for treating a disease state in a patient, wherein the disease is associated with a physiological detrimental level of insulin, glucose, free fatty acids (FFA), or triglycerides, in the blood, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, and also administering a therapeutically effective amount of a biguanidine compound.

In another aspect, the present invention provides a method for treating a disease state in a patient, wherein the disease is associated with a physiological detrimental level of insulin, glucose, free fatty acids (FFA), or triglycerides, in the blood, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, and also administering a therapeutically effective amount of metformin.

The invention also provides kits or single packages combining two or more active ingredients useful in treating the disease. A kit may provide (alone or in combination with a pharmaceutically acceptable diluent or carrier), a compound of Formula (I) and an additional hypoglycaemic agent (alone or in combination with diluent or carrier).

There are many known hypoglycemic agents in the art, for example, insulin; biguanidines, such as metformin and buformin; sulfonylureas, such as acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glypizide and glyclazide; thiazolidinediones, such as troglitazone; α-glycosidase inhibitors, such as acarbose and miglatol; and B_3 adrenoreceptor agonists such as CL-316, 243.

Since sulfonylureas are known to be capable of stimulating insulin release, but are not capable of acting on insulin resistance, and compounds of Formula I are able to act on insulin resistance, it is envisaged that a combination of these medicaments could be used as a remedy for conditions associated with both deficiency in insulin secretion and insulin-resistance.

Therefore, the invention also provides a method of treating diabetes mellitus of type II in a patient comprising administering a compound of Formula I and one or more additional hypoglycemic agents selected from the group consisting of sulfonylureas, biguanidines, thiazolidinediones, B_3-adrenoreceptor agonists, α-glycosidase inhibitors and insulin.

The invention also provides a method of treating diabetes mellitus of type II in a patient comprising administering a compound of Formula I and a sulfonylurea selected from the group consisting of acetohexamide, chlorpropamide, tolazamide, tolbutamide, glyburide, glypizide and glyclazide.

The invention also provides a method of treating diabetes mellitus of type II in a patient comprising administering a compound of Formula I and a biguanidine selected from the group consisting of metformin and buformin.

The invention also provides a method of treating diabetes mellitus of type II in a patient comprising administering a compound of Formula I and an α-glycosidase inhibitor selected from the group consisting acarbose and miglatol.

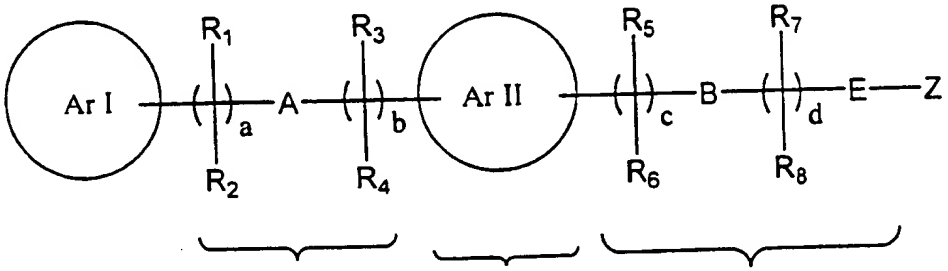
The invention also provides a method of treating diabetes mellitus of type II in a patient comprising administering a compound of Formula I and an thiazolidinedione, for example, troglitazone.

As indicated above, a compound of Formula I may be administered alone or in combination with one or more additional hypoglycemic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula I and one or more additional hypoglycemic agent, as well as administration of the compound of Formula I and each additional hypoglycemic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula I and hypoglycemic agent can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compound of Formula I and one or more additional hypoglycemic agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially.

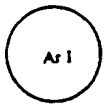
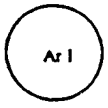
For example, the compound of Formula I may be administered in combination with one or more of the following additional hypoglycemic agents: insulin; biguanidines such as metformin or buformin; sulfonylureas such as acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glypizide or glyclazide; thiazolidinediones such as troglitazone; α-glycosidase inhibitors such as acarbose or miglatol; or B_3 adrenoreceptor agonists such as CL-316, 243.

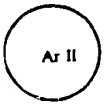
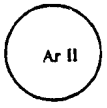
The compound of Formula I is preferably administered with a biguanidine, in particular, metformin.

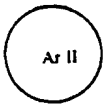
The compounds of Formula I contain at least two aromatic or hetero-aromatic rings, which may be designated as shown in Formula II below, and for which their substitution pattern along the chain with respect to each other also is shown below.



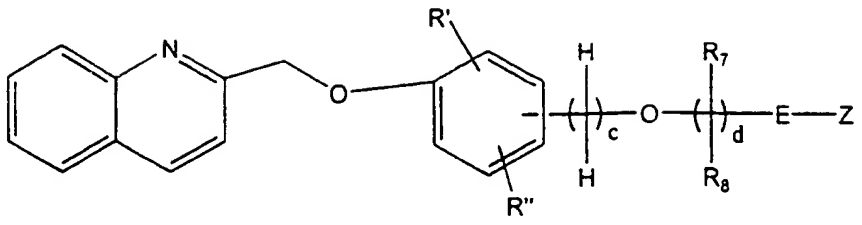
Ring I Linker I Ring II Linker II (II)

A preferred aspect of the compounds of Formula II, is a compound wherein  is selected from quinolinyl, benzothiophenyl, benzoimidazolyl, quinazolinyl, benzothiazolyl, quinoxalinyl, naphthyl, pyridyl,1H-indazolyl, 1,2,3,4-tetrahydroquinolinyl, benzofuranyl, thienyl, or indolyl, and one end of the linker, Linker I, is attached to  preferably at the 2-position of the ring moiety.

Another aspect of the compounds of Formula II is a compound wherein  is a 6-membered aryl or heteroaryl group and Linker I and Linker II are attached to  at positions 1,3-, or 1,4- to each other.

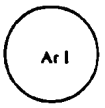
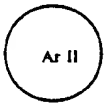
Another aspect of the compounds of Formula II is a compound wherein  is a naphthyl group, Linker I and Linker II are attached to  at positions 1,4-, or 2,4- to each other on the naphthyl moiety.

A further preferred aspect of the compound of Formula II is described by Formula V below:



(V)

where R_7, R_8, c, d, E and Z are as defined above, c + d = 1-3, and R' and R" are ring system substituents.

Another aspect of this invention is a compound of the invention wherein  is optionally substituted aryl, optionally substituted azaheteroaryl, or optionally substituted fused arylheterocyclenyl or fused arylheterocyclyl; and  is optionally substituted phenyl or optionally substituted naphthyl, optionally substituted heteroaryl, or optionally substituted fused arylheterocyclenyl.

Another aspect of this invention is a compound of the invention wherein a = 1 or 2; R_1 and R_2 is hydrogen; A is a chemical bond; and b = 0.

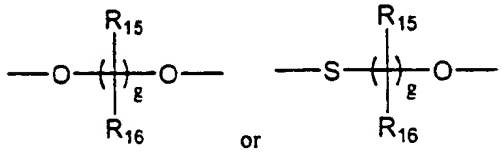
Another aspect of this invention is a compound of the invention wherein a = 0, 1, or 2, A is $-C(O)N(R^{15})-$ or $-N(R^{14})C(O)-$, and b = 0 or 1.

Another more preferred aspect of this invention is a compound of the invention wherein R_1 and R_2 are both hydrogen, a = 1, A is –O- and b = 0.

Another more preferred aspect of this invention is a compound of the invention wherein R_1 and R_2 are both hydrogen, a = 2, A is –O- and b = 0.

Another more preferred aspect of this invention is a compound of the invention wherein a = 0. A is –O- or $-NR_{13}-$; R_{13} is hydrogen or alkyl; R_3 and R_4 are both independently hydrogen; and b = 1.

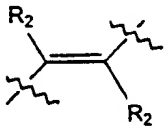
Another aspect of this invention is a compound of the invention wherein a = 0; A is



; R_{15} and R_{16} are hydrogen; g is 1, 2, 3 or 4; and b = 0.

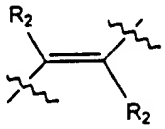
Another aspect of this invention is a compound of the invention wherein a = 0; A is $-NR_{13}-$, b = 1. R_3 and R_4 are hydrogen, and R_{13} is hydrogen, alkyl, or $R_{22}(O=)C-$.

Another aspect of this invention is a compound of the invention wherein a = 2; then the vicinal R_1 radicals taken together with the carbon atoms through which these radicals are linked form a



group; R_2 is hydrogen; A is a chemical bond or –O-; and b=0.

Another aspect of this invention is a compound of the invention wherein a = 6; then at least one pair of vicinal R_1 radicals taken together with the carbon atoms through which these radicals are linked form a

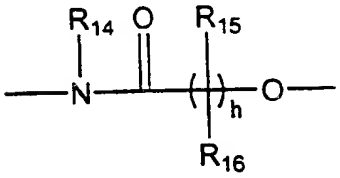


group; R_2 is hydrogen or alkyl; A is –O-; and b=0.

Another aspect of this invention is a compound of the invention wherein a = 1, 2 or 3; R_1 and R_2 are hydrogen; A is -O-; and b = 0.

Another aspect of this invention is a compound of the invention wherein a = 1; R_1, R_2, R_3 and R_4 are hydrogen; A is -O-; and b = 1.

Another aspect of this invention is a compound of the invention wherein a = 2; A is



; h = 1 or 2; and b = 0.

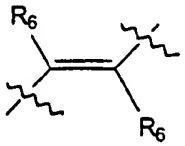
Another aspect of this invention is a compound of the invention wherein c = 0; d = 0; B and E is a chemical bond; Z is $R_{21}O_2SHNCO$-, and R_{21} is phenyl.

Another aspect of this invention is a compound of the invention wherein c = 0; d = 2; B is $–C(O)N(R_{20})$-, E is a chemical bond; Z is a tetrazolyl group or $–CO_2R_{21}$; R_{20} is hydrogen, alkyl, alkoxycarbonyl.

Another aspect of this invention is a compound of the invention wherein c = 0 or 4; d = 0 or 1; B and E is a chemical bond; Z is tetrazolyl, NH_2CO- or $–CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

Another aspect of this invention is a compound of the invention wherein c = 0 or 1; d = 0 or 1; B is –O- or a chemical bond; E is a chemical bond; and Z is tetrazolyl, NH_2CO- or $–CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

Another aspect of this invention is a compound of the invention wherein c = 0; d = 1; B is –O- or a chemical bond; E is a chemical bond; R_7 and R_8 are hydrogen or alkyl; and Z is tetrazolyl, NH_2CO- or $–CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

Another aspect of this invention is a compound of the invention wherein c = 2 or 4, then at least one pair of vicinal R_5 radicals taken together with the carbon atoms to which the R_5 radicals are linked form a  group; d = 0; D and E is a chemical bond; and Z is a tetrazolyl group or $-CO_2R_{21}$; and R_{21} is hydrogen.

Another aspect of this invention is a compound of the invention wherein c = 0; d = 3 or 4; B is -O-; E is a chemical bond; R_7 and R_8 are hydrogen or alkyl, or at least one of R_7 is carboxyl or alkoxycarbonyl; Z is tetrazolyl, $-CO_2R_{21}$ or $(R_{21})_2NC(O)-$; and R_{21} is hydrogen or lower alkyl.

Another aspect of this invention is a compound of the invention wherein c = 0; d = 1, 2, or 3; B is -C(O)-; E is a chemical bond; R_7 and R_8 are hydrogen or alkyl; Z is tetrazolyl or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

Another aspect of this invention is a compound of the invention wherein c = 4; d = 0; B and E are a chemical bond; R_7 and R_8 are hydrogen or alkyl; Z is tetrazolyl or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

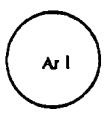
Another aspect of this invention is a compound of the invention wherein c = 0, 1 or 2; d = 1, 2 or 3; B is –S- or NR_{19}, E are a chemical bond; R_5, R_6, R_7 and R_8 are hydrogen; Z is tetrazolyl or $-CO_2R_{21}$; and R_{21} is hydrogen or lower alkyl.

Another aspect of this invention is a compound of the invention wherein R_6 and R_8 are $-(CH_2)q-X$; q is 0, 1 or 2; and X is independently hydrogen, aralkyl or lower alkyl.

Another aspect of this invention is a compound of the invention wherein at least one pair of geminal R_5 and R_6 radicals taken together with the carbon atom through which these radicals are linked form a 5-membered cycloalkyl group.

Another aspect of this invention is a compound of the invention wherein at least one pair of geminal R_7 and R_8 radicals taken together with the carbon atom through which these radicals are linked form a 5-membered cycloalkyl group.

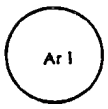
Another aspect of this invention is a compound of the invention wherein Z is $-CO_2H$, -CN or a tetrazolyl group.

A preferred aspect of this invention is a compound of the invention wherein 

is an optionally substituted quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, *N*-alkyl-quinolin-4-onyl, quinazolin-4-onyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl,

benzothiophenyl, indolinyl oxazolyl, thiazolyl, oxadiazolyl isoxazolyl, imidazolyl, pyrazol-yl, thiadiazolyl, triazolyl, pyridyl pyrimidinyl, pyrazinyl, pyridazinyl, phenyl, or napthalenyl group, wherein the substituent is a ring system substituent as defined herein, more preferably a substituent selected from the group consisting of phenyl, substituted-phenyl, thienyl, substituted thienyl, cycloalkyl, lower alkyl, branched alkyl, fluoro, chloro, alkoxy, aralkyloxy, trifluoromethyl and trifluoromethyloxy.

A more preferred aspect of this invention is a compound of the invention wherein

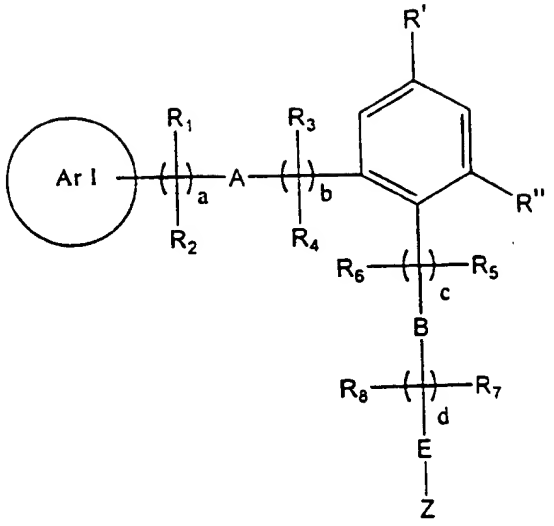


is unsubstituted quinolin-2-yl, 3-substituted quinolin-2-yl, 4-substituted quinolin-2-yl, 6-substituted quinolin-2-yl or 7 substituted quinolin-2-yl; an unsubstituted quinozalin-2-yl, 3-substituted quinozalin-2-yl, 6-substituted quinozalin-2-yl or 3,6-disubstituted quinozalin-2-yl; unsubstituted quinazolin-2-yl, 4-substituted quinazolin-2-yl or 6-substituted quinazolin-2-yl; unsubstituted isoquinolin-3-yl, 6-substituted isoquinolin-3-yl or 7-substituted isoquinolin-3-yl; 3-substituted-quinazolin-4-on-2-yl; *N*-substituted quinolin-4-on-2-yl; 2-substituted-oxazol-4-yl or 2,5 disubstituted-oxazol-4-yl; 4-substituted oxazol-2-yl or 4,5-disubstituted-oxazol-2-yl; 2-substituted thiazol-4-yl or 2,5-disubstituted thiazol-4-yl; 4-substituted thiazol-2-yl or 4,5-disubstituted-thiazol-2-yl; 5-substituted-[1,2,4]oxadiazol-3-yl; 3-substituted-[1,2,4] oxadiazol-5-yl; 5-substituted-imidazol-2-yl or 3,5-disubstituted-imidazol-2-yl; 2-substituted-imidazol-5-yl or 2,3-disubstituted-imidazol-5-yl; 3-substituted-isoxazol-5-yl; 5-substituted-isoxazol-3-yl; 5-substituted-[1,2,4] thiadiazol-3-yl; 3-substituted-[1,2,4]-thiadiazol-5-yl; 2-substituted-[1,3,4]-thiadiazol-5-yl; 2-substituted-[1,3,4]-oxadiazol-5-yl; 1-substituted-pyrazol-3-yl; 3-substituted-pyrazol-5-yl; 3-substituted-[1,2,4]-triazol-5-yl; 1-substituted-[1,2,4]-triazol-3-yl; 3-substituted pyridin-2-yl, 5-substituted pyridin-2-yl, 6-substituted pyridin-2-yl or 3,5-disubstituted pyridin-2-yl; 3-substituted pyrazin-2-yl, 5-substituted pyrazin-2-yl, 6-substituted pyrazin-2-yl or 3,5 disubstituted-pyrazin-2-yl; 5-substituted pyrimidin-2-yl or 6-substituted-pyrimidin-2-yl; 6-substituted-pyridazin-3-yl or 4,6-disubstituted-pyridazin-3-yl; unsubstituted napthalen-2-yl, 3-substituted napthalen-2-yl, 4-substituted napthalen-2-yl, 6-substituted napthalen-2-yl or 7 substituted napthalen-2-yl; 2-substituted phenyl, 4-substituted phenyl or 2,4-disubstituted phenyl; unsubstituted -benzothiazol-2-yl or 5-substituted-benzothiazol-2-yl; unsubstituted benzoxazol-2yl or 5-substituted-benzoxazol-2yl; unsubstituted -benzimidazol-2-yl or 5-substituted-benzimidazol-2-yl; unsubstituted -thiophen-2yl, 3-substituted -thiophen-2yl, 6-substituted -thiophen-2yl or 3,6-disubstituted-thiophen-2yl; unsubstituted -benzofuran-2-y, 3-substituted-

benzofuran-2-yl, 6-substituted-benzofuran-2-yl or 3,6-disubstituted-benzofuran-2-yl; 3-substituted-benzofuran-6-yl or 3,7-disubstituted-benzofuran-6-yl, wherein the substituent is a ring system substituent as defined herein, more preferably a substituent selected from the group consisting of phenyl, substituted-phenyl, thienyl, substituted thienyl, cycloalkyl, lower alkyl, branched alkyl, fluoro, chloro, alkoxy, aralkyloxy, trifluoromethyl and trifluoromethyloxy.

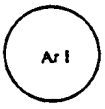
Another more preferred aspect of this invention is a compound of the invention wherein a = 0, A is –O- or $-NR_{13}-$; R_{13} is hydrogen or alkyl; R_3 and R_4 are both independently hydrogen; b = 1; and ArI is 3-substituted quinolin-2-yl, 4-substituted quinolin-2-yl, 6-substituted quinolin-2-yl, 7 substituted quinolin-2-yl, unsubstituted quinoxalin-2-yl, 3-substituted quinoxalin-2-yl, 6-substituted quinoxalin-2-yl, 3,6-disubstituted quinoxalin-2-yl, unsubstituted quinazolin-2-yl, 4-substituted quinazolin-2-yl, 6-substituted quinazolin-2-yl, unsubstituted isoquinolin-3-yl, 6-substituted isoquinolin-3-yl, 7-substituted isoquinolin-3-yl, 4-substituted oxazol-2-yl, 4,5-disubstituted-oxazol-2-yl, 4-substituted-thiazol-2-yl, 4,5-disubstituted-thiazol-2-yl, 5-substituted -imidazol-2-yl, 3,5-disubstituted-imidazol-2-yl, 1-substituted-pyrazol-3-yl, 3-substituted-pyrazol-5-yl, 3-substituted pyridin-2-yl, 5-substituted pyridin-2-yl, 6-substituted pyridin-2-yl or 3,5-disubstituted pyridin-2-yl, 3-substituted pyrazin-2-yl, 5-substituted pyrazin-2-yl, 6-substituted pyrazin-2-yl, 3,5 disubstituted-pyrazin-2-yl, 5-substituted pyrimidin-2-yl, 6-substituted-pyrimidin-2-yl, 6-substituted-pyridazin-3-yl, 4,6-disubstituted-pyridazin-3-yl, unsubstituted-benzothiazol-2-yl, 5-substituted-benzothiazol-2-yl, unsubstituted-benzoxazol-2-yl, 5-substituted-benzoxazol-2-yl, unsubstituted benzimidazol-2-yl, 5-substituted-benzimidazol-2-yl, 3-substituted-benzofuran-6-yl or 3,7-disubstituted-benzofuran-6-yl.

Another aspect of this invention is a compound of formula I as described by formula (Ia) below:



(Ia)

wherein



is independently aryl. fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

a = 1;

b = 0;

R_1 and R_2 are hydrogen

A is --O-;

R_5, R_6, R_7, R_8 are hydrogen;

c = 0;

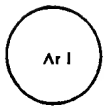
d = 0;

B and E are a chemical bond;

Z is $R_{21}O_2C$-, $R_{21}OC$-, cyclo-imide, -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$-, $R_{21}O$- 2,4-thiazolidinedionyl, or tetrazolyl;

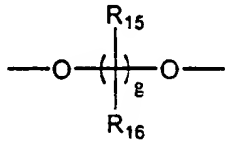
R' and R" are ring system substituents as defined herein, more preferably, R' is hydrogen, lower alkyl, halo, alkoxy, aryloxy or aralkyloxy; and R" is lower alkyl, hydrogen, aralkyloxy, alkoxy, cycloalkylalkyloxy or halo.

Another aspect of this invention is a compound of formula I as described by formula (Ia) wherein



is independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

a = 1;



A is ;

g = 2, 3, 4 or 5;

R_1, R_2, R_3, R_4, R_{15} and R_{16} are hydrogen;

b = 0 or 1;

c = 0;

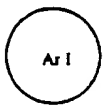
d = 0;

B and E are a chemical bond;

Z is $-CO_2H$;

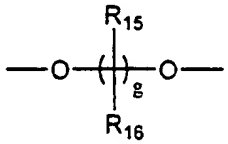
R' and R" are ring system substituents as defined herein, more preferably, R' is hydrogen, lower alkyl, halo, alkoxy, aryloxy or aralkyloxy; and R" is lower alkyl, alkoxy, aralkoxy, cycloalkylalkoxy or halo.

Another aspect of this invention is a compound of formula I as described by formula (Ia) wherein



is independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

a = 1;



A is ;

g = 2, 3, 4 or 5;

R_1, R_2, R_3, R_4, R_{15} and R_{16} are hydrogen;

b = 0 or 1;

c = 0;

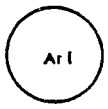
d = 0;

B and E are a chemical bond;

Z is $-CO_2H$;

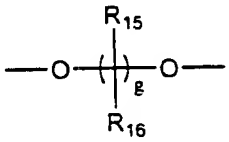
R' is hydrogen; and R" is lower alkyl.

Another aspect of this invention is a compound of formula I as described by formula (Ia) wherein



is independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl. or fused heteroarylheterocyclyl;

a = 1;

A is 

;

g = 2, 3, 4 or 5;

R_1, R_2, R_3, R_4, R_{15} and R_{16} are hydrogen;

R_7 and R_8 are independently hydrogen;

b = 0 or 1;

c = 0;

d = 1;

B and E are a chemical bond;

Z is $-CO_2H$;

R' and R" are ring system substituents as defined herein, more preferably, R' is hydrogen, lower alkyl, halo, alkoxy, aryloxy or aralkyloxy; and R" is lower alkyl, alkoxy, aralkoxy, cycloalkylalkoxy or halo.

Another aspect of this invention is a compound of formula I as described by formula (Ia) wherein